

### **Remarks**

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks presented herein, is respectfully requested. Claims 1, 10-11, and 42 are amended. The pending claims are claims 1, 3-4, 6-11, and 42-43. The amendments to the claims are intended to clarify Applicant's invention and are not intended to limit the equivalents to which any claim element may be entitled.

Amended claim 1 is supported by Table 3.

The amendment to claim 10 is supported by originally-filed claim 10.

The amendments to claim 11 are supported by originally-filed claim 11 and by the specification at page 19, lines 23-26.

The amendment to claim 42 is supported by the specification at page 118.

In the final Office Action, the Examiner objected to claims 9-10 under 37 C.F.R. § 1.75, asserting that claim 9 is a substantial duplicate of claim 10. The amendment to claim 10 renders the Examiner's objection moot.

The Examiner also objected to claims 42-43 under 37 C.F.R. § 1.821(d) in the final Office Action. With respect to claim 42, the Examiner requests that Applicant remove the recitation of the sequences from the claims and simply recite the SEQ ID number. 37 C.F.R. § 1.821(d) states that 'reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.' Thus, according to 37 C.F.R. § 1.821(d), it is permissible to recite both the sequence identifier and the sequence itself in a claim. However, for the sake of clarity, Applicant has amended claim 42. The amendment to claim 42 renders the Examiner's objection to claim 42 moot.

With respect to claim 43, in the final Office Action the Examiner asserted that this claim lacked a sequence identifier. Claim 43 is directed to a cyclic reverse sequence derivative (CRD) of a certain amino acid sequence. M.P.E.P. § 2421.02 states that "[t]he sequence rules embrace all...non-D amino acid sequences with four or more amino acids." M.P.E.P § 2422.01 explains the exclusion of D-amino acids from the rules by stating that "[t]he limitation to L-amino acids is based upon the fact that there currently exists no widely accepted standard nomenclature for representing the scope of amino acids encompassed by non-L-amino acids, and, as such, the

process of meaningfully encoding these other amino acids for computerized searching and printing is not currently feasible. The presence of one or more D-amino acids in a sequence will exclude that sequence from the scope of the rules.” Therefore, no sequence identifier is required for the amino acid sequence recited in claim 43.

#### The 35 U.S.C. § 112, Second Paragraph, Rejection

The Examiner rejected claims 11 and 43 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The amendments to claim 11 overcome this rejection, and so withdrawal of the § 112(2) rejection of the claims is respectfully requested.

#### The 35 U.S.C. § 112, First Paragraph, Rejection

The Examiner rejected claims 1, 3-4, 6-11, and 42-43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner asserts that although Applicant’s specification enables claims to the peptides set forth in sequence identifier numbers 1 and 7-14 and the CRD peptide set forth in sequence identifier number 14, the specification does not enable any other chemokine peptide. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

As evidence that Applicant’s disclosure would enable the art worker to prepare chemokine peptides, variants or derivatives thereof falling within the scope of the claims, the Examiner is respectfully requested to reconsider the pending claims in view of Applicant’s detailed specification. As amended, the claims are directed to an isolated and purified peptide of a chemokine, a variant, or a derivative thereof, comprising no more than 30 amino acid residues, wherein at least three contiguous residues of the peptide correspond to residues in the carboxyl-terminal half of the mature form of the chemokine, wherein the three contiguous residues correspond to residues Trp-Val-Gln (WVQ) or Lys-Gln-Lys (KQK) in human MCP-1, and wherein the peptide inhibits the activity of the corresponding native chemokine. For example, Table 3 shows an alignment of selected chemokines and indicates the general location of peptide

3 in human MCP-1, murine MCP-1, human MCP-2, human MCP-3, human MIP-1 $\alpha$ , human MCP-1 $\beta$ , RANTES, eotaxin, IL8, and human SDF-1 $\alpha$ . It is disclosed that cysteine residues are used to generally align the sequences. Exemplary chemokines, from which the peptides of the invention may be obtained or derived, are listed at page 17, lines 3-15 of the specification, and include MCP-1, MCP-2, MCP-3, MIG, MIP1 $\alpha$ , MIP1 $\beta$ , RANTES, PF-4, I-309, HCC-1, eotaxin, C10, CCR-2, ENA-78, GRO $\alpha$ , GRO $\beta$ , GRO $\gamma$ , IL-8, IP-10, SDF1 $\alpha$ , SDF1 $\beta$ , TARC, LARC, MIG, Ck $\beta$ 8, CCF18/MRP-2, MIP1 $\tau$ , and NAP-2.

It is further disclosed that a peptide of the invention may have 100% contiguous amino acid sequence homology or identity to the amino acid sequence of a native chemokine, or have less than 100% homology to the corresponding amino acid sequence of a nature chemokine, i.e., the peptide is a "variant" peptide. A variant peptide is disclosed as a peptide which has amino acid residues not present in the corresponding wild-type chemokine, e.g., amino acid substitution(s), internal deletion(s) or D-amino acid(s). Chemokine peptides or peptide variants which are subjected to chemical modifications, such as esterification, amidation, reduction, protection and the like, are referred to as chemokine "derivatives." For example, a modification known to improve the stability and bioavailability of peptides *in vivo* is the cyclization of the peptide. Thus, a derivative of a peptide of the invention may include a cyclic reverse sequence derivative (CRD), linear reverse D derivative (LRD) and cyclic forward L derivative (CFL) of a peptide of the invention.

Moreover, the specification provides exemplary *in vitro* and *in vivo* assays to identify whether a chemokine peptide, a variant thereof, or a derivative thereof, inhibits or reduces a chemokine-induced activity (page 27, lines 25-27). These assays include *in vitro* assays (see page 28, line 9-page 30, line 10) which detect whether an agent inhibits the chemokine-induced chemotaxis of a variety of cell types (e.g., neutrophils, monocytes, eosinophils, mast cells, platelets or lymphocytes; page 29, lines 12-13), inhibits the release of enzymes from certain cells (such as N-acetyl- $\beta$ -D-glucosamidase from monocytes or elastase from neutrophils; page 30, lines 13-24), changes the concentration of cytosolic free Ca<sup>2+</sup> in various cell types (monocytes, eosinophils, neutrophils; page 30, line 2-page 31, line 29), inhibits binding to a chemokine receptor and/or displaces bound chemokine (page 32, line 1-page 33, line 9), and inhibits the co-mitogenic activity of a chemokine (page 35, line 25-page 34, line 2).

Example 1 discloses the use of an *in vitro* chemotaxis assay, i.e., the inhibition of chemokine-induced THP-1 (a monocytic cell line) migration, to identify regions of human MCP-1 (hMCP1) falling within the scope of the invention. Example 4 describes that a CRD peptide variant of MCP-1 inhibited MCP-1-induced THP-1 migration. Table 4 shows the inhibition by a MCP-1 chemokine peptide 3 of the MCP-1-, MIP1 $\alpha$ -, IL8- and SDF-1 $\alpha$ -induced migration of THP-1 cells and primary human monocytes. Table 6 shows ED<sub>50</sub> data for four chemokines (MCP-1, MIP1 $\alpha$ , IL8 and SDF-1 $\alpha$ ) and selected peptides which include variants of MCP-1 chemokine peptide 3, e.g., one variant peptide of human MCP-1 chemokine peptide 3 (the variant is designated Leu<sub>4</sub>Ser<sub>7</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1]) has amino acid substitutions at positions 4, 7 and 11 relative to the sequence of a 12 amino acid peptide of human MCP-1 designated peptide 3(1-12)[MCP-1], and another variant (referred to as Ser<sub>7</sub>Glu<sub>8</sub>Glu<sub>9</sub>peptide3(1-12)[MCP-1]) has substitutions at positions 7, 8 and 9 relative to peptide 3(1-12)[MCP-1]. With regard to derivatives of the peptides of the invention, Example 4 describes the *in vitro* activity of a CRD, CFL, LRD and linear forward L (LFL) peptide of the invention.

Table 6 also includes data from three chemokine peptides having three amino acid residues, one of which is a tripeptide from MIP-1 $\alpha$ . Some of the peptides described in Table 6 were found to be pan-chemokine inhibitors, while others showed selectivity for certain groups of chemokines, i.e., selectivity for CC or CXC chemokines. Example 6 discloses additional experiments for tripeptides of the invention. Thus, the tripeptide WVQ, a sequence found in the carboxy-terminal half of MCP-1, MCP-3, MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, eotaxin and IL8, inhibited all four chemokines tested, while tripeptide KQK, another sequence found in the carboxy-terminal half of MCP-1, was specific for MCP-1 (versus MIP-1 $\alpha$ , IL8 or SDF-1 $\alpha$ ). It is disclosed that the corresponding tripeptides for MIP-1 $\alpha$  (SEE), SDF-1 (KLK), and IL8 (KEN) were each specific for the cognate chemokine.

It is further disclosed that the efficacy of a peptide of the invention in an animal model may be assessed by clinical parameters specific for the particular model or by general parameters such as the extent of inflammation or cellular infiltration into affected tissues (page 44, lines 14-15). Animal models which may be employed to determine whether a peptide of the invention inhibits chemokine-induced activity *in vivo* are exemplified at pages 43-46 of the specification. For example, atherosclerosis is associated with chemokine-induced, e.g., MCP-1-induced,

macrophage recruitment. Animal models of atherosclerosis include apoE knockout mice, mice which over express human apoB, and Watanabe heritable hyperlipidemic rabbits (page 44, lines 1-5). Animal models for autoimmune disease include collagen-induced arthritis in DBA/1 mice and myelin basic protein-induced experimental autoimmune encephalomyelitis. Animals models for osteoporosis include ovariectomized female rats, mice and monkeys, rats treated with heparin or glucocorticoids, and suspension-induced osteoporosis in rats. Thus, for atherosclerosis, the extent of lipid lesion formation in vessel walls may be determined in animals that have been administered a peptide of the invention relative to control animals (page 44, lines 23-27). For osteoporosis, bone density may be determined (page 78), as well as the presence bone matrix degradation products in plasma and urine (page 78), in animals that have been administered a peptide of the invention relative to control animals.

Therefore, Applicant has provided extensive guidance on how to identify peptides, including variant peptides and derivatives thereof, falling within the scope of the invention, as well as provided numerous working examples (factors 2-3 of Ex parte Forman, 230 U.S.P.Q. 546 (Bd. App. 1986), as summarized in In re Wands, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Thus, it is respectfully submitted that the enablement question in this case is very similar to that resolved by the Board of Appeals in Ex parte Mark, 12 U.S.P.Q.2d 1904 (Bd. App. 1989). The generic polypeptide was claimed as follows:

1. A synthetic mutein of a biologically active native protein in which native protein has a least one cysteine residue that is free to form a disulfide link and is nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.

Here, the "broader than the enabling disclosure" rejection was reversed, since the specification taught how to delete or replace cysteine residues and how to determine whether or not a given "mutein" was within the scope of the claims.

The Examiner alleges that the claims at issue are even broader than the claims in Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). The court in Amgen concluded that the specification in question was not enabling for a claim directed to nucleic acid molecules encoding a polypeptide having an amino acid sequence sufficiently

duplicative of EPO to have the property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake. In particular, the Amgen court noted that although the specification provided details for preparing a few EPO analogs, which may justify a generic claim encompassing these and similar analogs, it did not provide adequate support for claims directed to all EPO analogs. The court indicated that to support broader claims, the specification needed to provide more disclosure regarding the identification of various analogs, methods for making those analogs and the structural requirements for producing compounds with EPO-like activity. In contrast to the specification and claims at issue in Amgen, as described above, Applicant's specification contains detailed methods to identify peptides falling within the scope of the claims, methods to prepare those peptides and structural requirements for activity.

As there is a reasonable correlation between Applicant's specification and the scope of the claims, Applicant's specification is fully enabling.

The Examiner contends that the present application is unlike In re Wands because 1) the "success" rate for identifying a hybridoma secreting the desired antibody in In re Wands was high, and 2) the claims in In re Wands were directed to a process and Wands' application described a repeatable process to obtain the hybridoma. The claims at issue in In re Wands were directed to 1) an immunoassay method which employed a IgM monoclonal antibody having a specific binding affinity for a viral surface antigen, and 2) chemically modified monoclonal IgM antibodies for use in the assays. From 6 different fusions, hybridomas were identified that secreted antibodies that had a high binding affinity for the viral antigen. Nine antibodies were subjected to an analysis to determine their specific binding affinity and 4 were found to have an affinity falling within the scope of the claims.

The PTO argued that the success rate was 4/143 (2.8%), while Wands argued that it was 4/9 (44%). The court noted that even if they were to accept the 2.8% success rate (which they did not), they would not be required to reach a conclusion of undue experimentation and that such a determination cannot be made solely by reference to a particular numerical cutoff (see footnote 29). Based on the considerable direction and guidance in Wands' specification on how to practice the invention and the presence of working examples, the high level of skill in the art, the fact that methods to prepare and identify the desired antibodies were known to the art, that

practitioners in the art were prepared to screen negative hybridomas in order to find a positive one, and that Wands had prepared an antibody falling within the scope of the claims on three separate occasions, the court concluded that it would not require undue experimentation to obtain the antibodies needed to practice the claimed invention.

Similarly, Applicant provides considerable direction and guidance on how to practice the claimed invention, provides working examples, and on multiple occasions prepared peptides falling within the scope of the claims. Moreover, methods to prepare peptides, variants thereof and derivatives thereof, and to screen those peptides, variants thereof and derivatives thereof, to determine whether they inhibit the activity of a particular chemokine, were well known to the art.

Further, the fact that the outcome of such a synthesis/screening program is unpredictable is precisely why a screening program is carried out. The Examiner simply cannot reasonably contend that a screening program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required to carry out extensive synthesis and screening programs to locate bioactive molecules do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to prepare and screen chemokine peptides, variant chemokine peptides and derivatives thereof to locate additional peptides falling within the scope of the claims. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a large number of peptides is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Forman, factors 4-6).

Even if, assuming for the sake of argument, it is not routine to screen large numbers of samples of individual chemokine peptides, variants thereof or derivatives thereof, a population of pooled peptides could be readily screened using one or more of the assays described in Applicant's specification for the presence of a peptide which inhibits or reduces a chemokine-induced activity. The samples which contributed to the pool with the desired phenotype are then screened individually to identify a peptide or derivative thereof which inhibits or reduces a chemokine-induced activity.

The Examiner asserts that the results at page 104 of Applicant's specification support the unpredictability of the inhibitory activity of chemokine peptide variants. Nevertheless, both peptide 3(1-6) and peptide 3(7-12) inhibited the activity of peptide 3(1-12), although to differing degrees. The Examiner is respectfully reminded that there is no requirement that all of the compounds within a claimed genus exhibit the same degree of efficacy in order to meet the requirements of 35 U.S.C. § 112. In re Gardner, 475 F.2d 1389, 177 U.S.P.Q. 396, 398 (C.C.P.A. 1973). If Applicant has provided the art worker with sufficient guidance on how to identify those peptides, Applicant has complied with the requirements of § 112(1).

The Examiner has urged that the following references support the assertion that it would require undue experimentation by the art worker to predict which changes can be tolerated in a protein while retaining activity: Cunningham et al. (Science, 244, 1081 (1988)), George et al. (In: Macromolecular Sequencing and Synthesis, pp. 127-149, Alan Liss, Inc. NY (1989)) and Bowie et al. (Science, 247, 1306 (1990)).

Cunningham et al. disclose that 62 single alanine substitutions were introduced into hGH at positions 2-19, 54-74 and 167-191, positions which had been implicated in receptor recognition. The authors note that "[a]lanine-scanning mutagenesis generates a small and systematic set of mutant proteins that can be readily assayed by quantitative binding analysis" (page 1081). A number of the substitutions resulted in a protein having a lower binding affinity to hGH receptor (Figure 1).

However, the fact that single amino acid substitutions of alanine in hGH may result in changes in receptor binding affinity, does not provide evidence that it would require undue experimentation by the art worker to reasonably predict positions in the protein that would tolerate changes without substantially changing the activity. Indeed, the alanine substituted



hGH mutants still bound to the hGH receptor, many with a reduced affinity, some with an increased affinity, and still others with an affinity that was similar to wild-type hGH. Further, based on the binding of the mutants to eight different monoclonal antibodies and circular dichroic spectra, the authors concluded that "it is unlikely" that the substitutions caused major tertiary structural changes, but more likely "small and local structural perturbations" (page 244). Moreover, Cunningham et al. clearly illustrates that, even in 1988, it was within the skill of the art to determine whether a large number of structurally related polypeptides had a certain activity.

The Examiner contends that Cunningham intentionally chose to mutate those residues implicated in receptor binding and that Applicant, unlike Cunningham, has not disclosed which regions are important for chemokine peptide function. However, the Examiner is respectfully referred to Examples 1-6 of Applicant's specification, which describe the chemokine inhibitory activity of peptide 3 relative to peptide 1 (which includes sequences from the amino terminus of the mature form of MCP-1) and peptide 2 (which includes sequences in the amino terminal half of the mature form of MCP-1), and the inhibitory activity of other chemokine peptides, including tripeptides of the invention, variants and derivatives thereof.

The George et al. paper relates to current methods for sequence comparison and analysis. While page 145 of George et al. discloses that sequence comparison methods will not be able to assess biological relatedness until the structure/function problem is more clearly understood, this disclosure was made in the context of using database-searching and sequence comparison methods to find sequences that best match a given test sequence or to find the best alignment between sequences. After noting that sequence comparison is more of a qualitative science than a quantitative science (page 146), George et al. disclose that statistical measures of similarity do not necessarily reflect biological significance. Nonetheless, there is nothing in George et al. to support the assertion that the art worker would engage in undue experimentation to predictably prepare a variant peptide having a particular activity.

With regard to the results from a number of studies in which amino acid changes were introduced to proteins, Bowie et al. conclude "that proteins are surprisingly tolerant of amino acid substitutions" (page 306). For example, Bowie et al. point to a study in which one-half of the substitutions at 142 positions in the *lac* repressor were phenotypically silent. At some

positions, nonconservative substitutions were allowed while at some residues, substitutions were not tolerated and or tolerated only if they were conservative (page 1306). Thus, Bowie et al. evidence that there is a reasonable expectation that any particular protein sequence can tolerate amino acid substitutions without significantly altering the activity of the substituted protein.

The Examiner is reminded that the "predictability or lack thereof" in the art refers to the ability of the art worker to extrapolate the disclosed or known results to the claimed invention. M.P.E.P. 2164.03. Despite the alleged unpredictability in this art, Applicant has structurally defined members of the claimed genus. Note that all of the tested peptides with the defined structure, which included substituted (variant) MCP-1 peptides at positions 4, 7, 8, 9, and 11, peptides of MIP1 $\alpha$ , SDF1 $\alpha$  (SDF1 is a CXC chemokine) and IL-8 (IL-8 is a CXC chemokine) and peptide derivatives, had activity (see Table 6, Example 4 and Example 6).

Thus, one of ordinary skill in the art in possession of Applicant's specification would find it reasonably predictable to prepare peptides, including variant peptides, having chemokine inhibitory activity and so would not engage in undue experimentation to prepare peptides falling within the scope of the claims.

In the Advisory Action, the Examiner asserts that claim 6, which depends on claim 1, is "broader" than claim 1 and does not further limit claim 1. Claim 1 is directed to an isolated and purified peptide of a chemokine, a variant, or a derivative thereof, comprising no more than 30 amino acid residues, wherein at least three contiguous residues of the peptide correspond to residues in the carboxyl-terminal half of the mature form of the chemokine, wherein the three contiguous residues correspond to residues Trp-Val-Gln or Lys-Gln-Lys in human MCP-1, and wherein the peptide inhibits the activity of the corresponding native chemokine. Claim 6 is directed to a peptide of a CC chemokine, a variant, or a derivative thereof, comprising no more than 30 amino acid residues, wherein at least three contiguous residues of the peptide correspond to residues in the carboxyl-terminal half of the mature form of the chemokine, wherein the three contiguous residues correspond to residues Trp-Val-Gln or Lys-Gln-Lys in human MCP-1, and wherein the peptide inhibits the activity of the corresponding native chemokine.

It is well known in the art that in the chemokine superfamily, there are distinct classes of chemokines defined by the arrangement of the conserved cysteine (C) residues of the mature proteins. For example, the CXC chemokines have one amino acid residue separating the first

two cysteine residues; the CC chemokines have the first two cysteine residues adjacent to each other; and the C chemokines lack two (the first and third) of the four conserved cysteine residues. Thus, claim 6 further limits claim 1.

Based on the remarks presented herein, it is respectfully submitted that the pending claims are in conformance with 35 U.S.C. § 112, first paragraph. Thus, withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph, is respectfully requested.

#### The 35 U.S.C. § 102(b) Rejection

In the Office Action dated April 7, 1999, the Examiner rejected claims 1, 3-4 and 6-7 under 35 U.S.C. § 102(b) as anticipated by Rollins et al. (U.S. Patent No. 5,459,128). In the final Office Action dated November 12, 1999, the Examiner indicated that the rejection of claims 1, 3-4 and 6-7 under 35 U.S.C. § 102(b) as anticipated by Rollins et al. was withdrawn (page 2 of that Office Action). However, in the Advisory Action, the Examiner indicates that the "102(b) rejection over claims 3-4 and 6-7 has not been obviated by the amendment". This rejection is respectfully traversed.

The mature form of MCP-1 has about 78 amino acids and attracts and activates monocytes. The Rollins et al. patent generally discloses MCP-1 "derivatives", i.e., MCP-1 derived polypeptides having amino acid substitutions or deletions, or insertions of an epitope tag, relative to the mature form of MCP-1. Preferred MCP-1 derivatives are disclosed as those with changes at amino acid position 3, 24 or 28, or which lack amino acids 2-8, of MCP-1. It is also disclosed that useful MCP-1 derivatives are those having decreased or no chemoattractant activity relative to MCP-1 and which inhibit the activity of MCP-1.

Figure 2 of the Rollins et al. patent shows the monocyte chemoattractant activity of 12 MCP-1 derivatives relative to wild-type MCP-1. Ten out of twelve of the derivatives had less than 60% of the chemoattractant activity of MCP-1. Four of the derivatives which had less than 10% of the chemoattractant activity of wild-type MCP-1 were tested in a dose response assay for their ability to inhibit monocyte chemotaxis in the presence of FX2, a derivative of wild-type MCP-1 having a carboxy-terminal epitope tag and 92% of the chemoattractant activity of wild-type MCP-1. The four derivatives were 7ND (a derivative which lacks residues 2-8 of MCP-1 and has a C-terminal epitope tag), D3A (a derivative with a D to A substitution at position 3 and

a C-terminal epitope tag), R24F (a derivative with a R to F substitution at position 24 and a C-terminal epitope tag), and Y28D (a derivative with a Y to D substitution at position 28 and a C-terminal epitope tag). Only two of the derivatives, 7ND and Y28D, reduced MCP-1-induced migration in a dose dependent manner.

Although Rollins et al. indicate that in MCP-1 derivatives other than those which encode D at position 3, R at position 24, D at position 28, and a deletion of residues 2-8, of MCP-1 are envisioned, the only derivatives disclosed in Rollins et al. which lack or have decreased chemoattractant activity relative to MCP-1 and which inhibit the monocyte chemoattractant activity of MCP-1 were Y28D and 7ND (see Figure 3 of Rollins et al.). Note that at higher concentrations, R24F and D3A increased MCP-1-induced migration of monocytes. Thus, the only derivatives in the Rollins et al. patent having the disclosed desired properties, i.e., no or reduced chemoattractant activity relative to MCP-1 and inhibition of MCP-1-induced migration, are derivatives that are about 71-78 amino acid residues in length and have modifications in the amino-terminal half of the mature form of MCP-1.

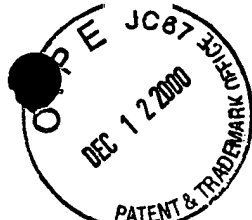
Rollins et al. do not disclose or suggest that a portion of a chemokine having less than 30 amino acid residues, e.g., a CC chemokine peptide having less than 30 amino acid residues (claims 6-7), a variant of a MCP-1 peptide having less than 30 amino acid residues (claim 4), or a chemokine peptide that is not a peptide of IL-8 or NAP-2 and which has less than 30 amino acid residues (claim 3), would inhibit the activity of the corresponding native chemokine. Therefore, the Rollins et al. patent does not anticipate Applicant's invention.

**PRELIMINARY AMENDMENT**

Serial Number: 08/927,939

Filing Date: September 11, 1997

Title: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE



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D.t.: 295.022US1

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**Conclusion**

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Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at the below-listed number to facilitate prosecution of this application. If necessary, please charge any additional fees deemed necessary to Deposit Account 19-0743. **TECH CENTER 1600/2900**

Respectfully submitted,

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